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NEWS	1		Web Page for STN Seminar Schedule - N. America
NEWS	2	APR 02	CAS Registry Number Crossover Limits Increased to 500,000 in Key STN Databases
NEWS	3	APR 02	PATDPAFULL: Application and priority number formats enhanced
NEWS	4	APR 02	DWPI: New display format ALLSTR available
NEWS	5	APR 02	New Thesaurus Added to Derwent Databases for Smooth Sailing through U.S. Patent Codes
NEWS	6	APR 02	EMBASE Adds Unique Records from MEDLINE, Expanding Coverage back to 1948
NEWS	7	APR 07	50,000 World Traditional Medicine (WTM) Patents Now Available in CAplus
NEWS	8	APR 07	MEDLINE Coverage Is Extended Back to 1947
NEWS	9	JUN 16	WPI First View (File WPIFV) will no longer be available after July 30, 2010
NEWS	10	JUN 18	DWPI: New coverage - French Granted Patents
NEWS	11	JUN 18	CAS and FIZ Karlsruhe announce plans for a new STN platform
NEWS	12	JUN 18	IPC codes have been added to the INSPEC backfile (1969-2009)
NEWS	13	JUN 21	Removal of Pre-IPC 8 data fields streamline displays in CA/CAplus, CASREACT, and MARPAT
NEWS	14	JUN 21	Access an additional 1.8 million records exclusively enhanced with 1.9 million CAS Registry Numbers -- EMBASE Classic on STN
NEWS	15	JUN 28	Introducing "CAS Chemistry Research Report": 40 Years of Biofuel Research Reveal China Now Atop U.S. in Patenting and Commercialization of Bioethanol
NEWS	16	JUN 29	Enhanced Batch Search Options in DGENE, USGENE, and PCTGEN
NEWS	17	JUL 19	Enhancement of citation information in INPADOC databases provides new, more efficient competitor analyses
NEWS	18	JUL 26	CAS coverage of global patent authorities has expanded to 61 with the addition of Costa Rica
NEWS	19	SEP 15	MEDLINE Cited References provide additional relevant records with no additional searching.
NEWS	20	OCT 04	Removal of Pre-IPC 8 data fields streamlines displays in USPATFULL, USPAT2, and USPATOLD.
NEWS	21	OCT 04	Precision of EMBASE searching enhanced with new chemical name field
NEWS	22	OCT 06	Increase your retrieval consistency with new formats for Taiwanese application numbers in CA/CAplus.

NEWS EXPRESS FEBRUARY 15 10 CURRENT WINDOWS VERSION IS V8.4.2,  
AND CURRENT DISCOVER FILE IS DATED 07 JULY 2010.

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FILE 'HOME' ENTERED AT 09:49:41 ON 20 OCT 2010

=> file registry

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.22	0.22

FILE 'REGISTRY' ENTERED AT 09:50:15 ON 20 OCT 2010

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STRUCTURE FILE UPDATES: 19 OCT 2010 HIGHEST RN 1246608-36-5

DICTIONARY FILE UPDATES: 19 OCT 2010 HIGHEST RN 1246608-36-5

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<http://www.cas.org/support/stngen/stndoc/properties.html>

=> e levosimendan

E1	1	LEVOSEMOTIADI/BI
E2	1	LEVOSEMOTIADIL/BI
E3	1 -->	LEVOSIMENDAN/BI
E4	1	LEVOSIN/BI
E5	1	LEVOSINUM/BI
E6	1	LEVOSPASME/BI
E7	1	LEVOSTARCH/BI
E8	1	LEVOSULFIN/BI
E9	1	LEVOSULP/BI
E10	1	LEVOSULPIRID/BI
E11	1	LEVOSULPIRIDE/BI
E12	5	LEVOTAN/BI

=> s e3

L1 1 LEVOSIMENDAN/BI

=> d 11

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2010 ACS on STN

RN 141505-33-1 REGISTRY

ED Entered STN: 22 May 1992

CN Propanedinitrile, 2-[2-[4-[(4R)-1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl]phenyl]hydrazinylidene]- (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Propanedinitrile, [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]-, (R)-

CN Propanedinitrile, [[4-[(4R)-1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl]phenyl]hydrazono]- (9CI)

OTHER NAMES:

CN (-)-OR 1259

CN (R)-Simendan

CN Levosimendan

CN OR 1259

CN Simdax

FS STEREOSEARCH

MF C14 H12 N6 O

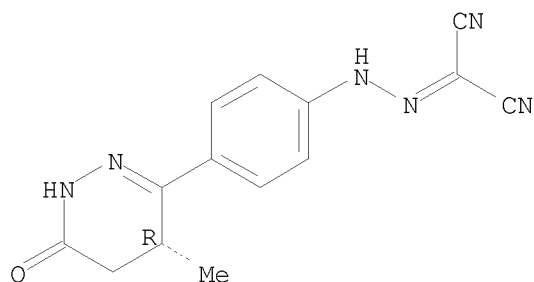
CI COM

SR World Health Organization (WHO)

LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSPRODUCT, IMSRESEARCH, IPA, MEDLINE, MRCK\*, PROMT, PROUSDDR, PS, RTECS\*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL

(\*File contains numerically searchable property data)

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

446 REFERENCES IN FILE CA (1907 TO DATE)

7 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

450 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus medline

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

8.09

8.31

FILE 'CAPLUS' ENTERED AT 09:50:42 ON 20 OCT 2010

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FILE 'MEDLINE' ENTERED AT 09:50:42 ON 20 OCT 2010

=> s (l1 or levosimendan) and (kidney or renal)  
L2 61 (L1 OR LEVOSIMENDAN) AND (KIDNEY OR RENAL)

=> s (l1 or levosimendan) (s) (kidney or renal)  
L3 29 (L1 OR LEVOSIMENDAN) (S) (KIDNEY OR RENAL)

=> dup rem l3  
PROCESSING COMPLETED FOR L3  
L4 21 DUP REM L3 (8 DUPLICATES REMOVED)

=> d l4 ibib abs 1-21

L4 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2010:1177487 CAPLUS  
TITLE: Effects of combined arginine vasopressin and  
levosimendan on organ function in ovine septic shock  
AUTHOR(S): Rehberg, Sebastian; Ertmer, Christian; Vincent,  
Jean-L.; Spiegel, Hans-U.; Koehler, Gabriele; Erren,  
Michael; Lange, Matthias; Morelli, Andrea; Seisel,  
Jennifer; Su, Fuhong; Van Aken, Hugo; Traber, Daniel  
L.; Westphal, Martin  
CORPORATE SOURCE: Departments of Anesthesiology and Intensive Care,  
University of Muenster, Muenster, Germany  
SOURCE: Critical Care Medicine (2010), 38(10), 2016-2023  
CODEN: CCMDC7; ISSN: 0090-3493  
PUBLISHER: Lippincott Williams & Wilkins  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Objective: To compare the effects of a first-line therapy of combined  
arginine vasopressin, levosimendan, and norepinephrine with arginine  
vasopressin + norepinephrine or norepinephrine alone in ovine septic  
shock. Design: Prospective, randomized, controlled laboratory experiment

Setting:

University animal research facility. Subjects: Twenty-one chronically  
instrumented sheep. Interventions: After the onset of fecal  
peritonitis-induced septic shock (mean arterial pressure <60 mm Hg), sheep  
were randomly assigned to receive first-line treatment with arginine  
vasopressin (0.5 mU·kg·min), combined arginine vasopressin  
(0.5 mU·kg·min) and levosimendan (0.2  
µg·kg·min), or normal saline (each n = 7) for 24 h. In  
all groups, open-label norepinephrine was addnl. titrated to maintain mean  
arterial pressure at 70 ± 5 mm Hg, if necessary. Measurements and main  
results: Arginine vasopressin + levosimendan + norepinephrine improved  
left ventricular contractility (higher stroke work indexes at similar or  
lower preload) and pulmonary function (Pao2/Fio2 ratio) when compared with  
the other groups (p < .05 each). Both nonadrenergic treatment strategies  
reduced open-label norepinephrine doses. However, only arginine  
vasopressin + levosimendan + norepinephrine limited fluid requirements and  
pos. fluid balance vs. both other groups (p < .05 each). In addition,  
arginine vasopressin + levosimendan + norepinephrine increased mixed  
venous oxygen saturation as compared with arginine vasopressin +  
norepinephrine. Histol. tissue analyses and pulmonary hemeoxygenase-1  
activity revealed no differences among groups. Notably, arginine  
vasopressin + levosimendan + norepinephrine therapy reduced pulmonary  
3-nitrotyrosine levels (p = .028 vs. control animals) as well as urinary  
protein/creatinine ratio (p < .05 each) and slightly prolonged survival

when compared with both other groups (4 h vs. arginine vasopressin + norepinephrine:  $p = .013$ ; 7 h vs. norepinephrine alone:  $p = .003$ ).  
Conclusions: First-line cardiovascular support with combined arginine vasopressin and levosimendan supplemented with norepinephrine improves myocardial, vascular, pulmonary, and renal function as compared with arginine vasopressin + norepinephrine in septic shock.

L4 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2009:1132679 CAPLUS

DOCUMENT NUMBER: 151:349929

TITLE: Reducing the risk of major elective non-cardiac surgery: is there a role for levosimendan in the preoperative optimization of cardiac function?

AUTHOR(S): Morelli, A.; Ertmer, C.; Pietropaoli, P.; Westphal, M.

CORPORATE SOURCE: Department of Anesthesiology and Intensive Care, University of Rome, "La Sapienza", Rome, Italy

SOURCE: Current Drug Targets (2009), 10(9), 863-871

CODEN: CDTUAA; ISSN: 1389-4501

PUBLISHER: Bentham Science Publishers Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Patients with heart failure undergoing non-cardiac surgery still have an unacceptably high morbidity and mortality. Compromised myocardial physiol. reserves in combination with extensive surgery and anesthesia appear to play a crucial role in determining high perioperative morbidity and mortality. Nevertheless, several other mechanisms and pathways such as metabolic factors, ischemia-reperfusion conditions, neurohormonal activation, inflammation and oxidative stress contribute to the adverse outcome. Several cardiovascular drugs have been investigated with the attempt to reduce the incidence of cardiovascular adverse events after major non-cardiac surgery. In the last years, increasing attention has been paid to the use of levosimendan in the perioperative period of patients undergoing cardiac surgery. As an inodilator, levosimendan - at low energy expenditure - may improve perioperative cardiac performance of heart failure patients by optimizing ventriculo-arterial coupling, rather than by increasing myocardial contractility itself. By its vasodilating properties, levosimendan may also improve systemic and regional blood flow. In addition to these hemodynamic properties, non hemodynamic effects of levosimendan may further improve microcirculation and organ function. At the cellular level in the heart, kidney, lung, liver as well as the gut, levosimendan exerts protective preconditioning effects secondary to activation of ATP-sensitive potassium channels. Taking into account these multiple but complementary mechanisms, levosimendan appears to be a suitable agent for preoperative optimization of cardiac functions in heart failure patients undergoing major elective surgery. Nevertheless, large-scale trials are needed before final conclusions can be drawn on the use of levosimendan in this indication.

REFERENCE COUNT: 111 THERE ARE 111 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L4 ANSWER 3 OF 21 MEDLINE on STN

ACCESSION NUMBER: 2009794139 MEDLINE

DOCUMENT NUMBER: PubMed ID: 19936016

TITLE: [Use of levosimendan in acute heart failure and its effect on renal function].  
Utilidad de Levosimendan en insuficiencia cardiaca aguda y su efecto sobre la funcion renal

AUTHOR: Moyano A Polo; Hidalgo R Lopez; Grande D Barreda; Morales S Cerezo

SOURCE: Nefrologia : publicacion oficial de la Sociedad Espanola

Nefrologia, (2009) Vol. 29, No. 6, pp. 616-7.  
Journal code: 8301215. ISSN: 0211-6995. L-ISSN: 0211-6995.  
PUB. COUNTRY: Spain  
DOCUMENT TYPE: (CASE REPORTS)  
Letter  
LANGUAGE: Spanish  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 201001  
ENTRY DATE: Entered STN: 3 Dec 2009  
Last Updated on STN: 27 Jan 2010  
Entered Medline: 26 Jan 2010

L4 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2009:29522 CAPLUS  
DOCUMENT NUMBER: 150:530049  
TITLE: Levosimendan and calcium sensitization of the  
contractile proteins in cardiac muscle: impact on  
heart failure  
AUTHOR(S): Kota, Bindu; Prasad, Aditya S.; Economides, Christina;  
Singh, Bramah N.  
CORPORATE SOURCE: West LA VA Medical Center, Los Angeles, CA, USA  
SOURCE: Journal of Cardiovascular Pharmacology and  
Therapeutics (2008), 13(4), 269-278  
CODEN: JCPTFE; ISSN: 1074-2484  
PUBLISHER: Sage Publications  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English

AB A review. Levosimendan increases the sensitivity of the cardiac fibrils to calcium, favorably affects hemodynamics in patients with heart failure. It is a pos. inotrope and a peripheral vasodilator. The elimination half-life of the compound is about 1 h. The drug decreases pulmonary capillary wedge pressure, increases cardiac output with the improvement in left ventricular ejection fraction leading to symptomatic improvement which includes decreased dyspnea and fatigue. Levosimendan can be used safely with diuretics, nitrates, beta-blockers, digoxin, and angiotensin-converting enzyme inhibitors. The most common adverse effects of levosimendan are headache and hypotension. Prolongation of the QTc interval does not appear to increase the incidence of arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Levosimendan is a novel agent in the treatment of decompensated heart failure, representing a newer class of medications aimed at increasing calcium sensitivity. Its properties holds promise for the treatment of heart failure but further large-scale studies will be needed to determine its precise efficacy, safety, as well as the compound's long-term impact on mortality.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD  
(1 CITINGS)  
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 21 MEDLINE on STN

ACCESSION NUMBER: 2008220845 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 18056154  
TITLE: The influence of levosimendan and iloprost on  
renal ischemia-reperfusion: an experimental study.  
AUTHOR: Yakut Necmettin; Yasa Haydar; Bahriye Lafci Banu; Ortac  
Ragip; Tulukoglu Engin; Aksun Murat; Ozbek Cengiz; Gurbuz  
Ali  
CORPORATE SOURCE: Department of Cardiovascular Surgery, Ataturk Education and  
Research Hospital, Izmir, Turkey.  
SOURCE: Interactive cardiovascular and thoracic surgery, (2008 Apr)  
Vol. 7, No. 2, pp. 235-9. Electronic Publication:

2007-12-03.

Journal code: 101158399. E-ISSN: 1569-9285. L-ISSN: 1569-9285.

PUB. COUNTRY: England: United Kingdom  
DOCUMENT TYPE: (COMPARATIVE STUDY)  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200805  
ENTRY DATE: Entered STN: 3 Apr 2008  
Last Updated on STN: 9 May 2008  
Entered Medline: 8 May 2008

AB The effects of iloprost on ischemia-reperfusion injury have been studied on the skeletal, muscle, liver, myocardium, kidney, and spinal cord. However, no sufficient data exist about effects of levosimendan on renal ischemia-reperfusion injury. The purpose of this experimental study was to investigate and compare effectiveness of levosimendan and iloprost on renal injury induced by ischemia and reperfusion. Fifty rabbits were divided into five groups. Levosimendan was continuously infused starting half an hour before the cross-clamp. Cross-clamp time was one hour. After one hour ischemia, levosimendan was continued for 4 h in Group A whereas Group B took iloprost in the same protocol. Group C was the control group which did not receive any medication. Group D was sham group and Group E was medicated both iloprost and levosimendan. Renal tissues were histologically and biochemically evaluated. The histological scores were obtained according to presence of tubular necrosis and atrophy, regenerative atypia, hydropic degeneration (Group A vs. Group C<0.001, Group B vs. Group C<0.001, Group D vs. Group C<0.01, Group E vs. Group C<0.001). Mean malondialdehyde levels were 114+/-12 nmol/g tissue; in Group A 121+/-13 nmol/g tissue, in Group B 134+/-13 nmol/g tissue, in Group E 130+/-11 nmol/g tissue, in Group D 134+/-11 nmol/g tissue (Group A vs. Group B; P=0.003, Group B vs. Group D; P=0.132, Group A vs. Group E; P=0.132). Malondialdehyde levels and histologic scores of all of the groups were significantly different from the control group. Iloprost and pentoxifyllin reduced renal ischemia-reperfusion injury in rabbit model. There was no significant difference between these two medications.

L4 ANSWER 6 OF 21 MEDLINE on STN  
ACCESSION NUMBER: 2008281242 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 18443483  
TITLE: Role of levosimendan in sepsis and septic shock.  
AUTHOR: Pinto Bernardo Bollen; Rehberg Sebastian; Ertmer Christian; Westphal Martin  
CORPORATE SOURCE: Department of Anesthesiology and Intensive Care, University Hospital of Muenster, Muenster, Germany..  
bollenpinto@gmail.com  
SOURCE: Current opinion in anaesthesiology, (2008 Apr) Vol. 21, No. 2, pp. 168-77. Ref: 84  
Journal code: 8813436. ISSN: 0952-7907. L-ISSN: 0952-7907.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200805  
ENTRY DATE: Entered STN: 30 Apr 2008  
Last Updated on STN: 14 May 2008  
Entered Medline: 13 May 2008

REFERENCE COUNT: 84 There are 84 cited references for this document.

AB PURPOSE OF REVIEW: To present the pharmacologic and biologic profile of levosimendan and discuss potential indications in the treatment of sepsis

and septic shock, with a special focus on myocardial and pulmonary dysfunction. RECENT FINDINGS: In animal models of endotoxic shock, levosimendan improved both left ventricular systolic and diastolic dysfunction, as well as ventriculovascular coupling. In addition, positive effects have been reported on right ventricular performance and pulmonary circulation. Two randomized, controlled trials in patients with septic shock revealed levosimendan provided consistent beneficial effects on cardiopulmonary performance, global oxygen transport, splanchnic perfusion and renal function. These effects have been reported as superior to placebo and the classic inotropic agent dobutamine. Due to its vasodilatory effects, combination with vasoconstrictor agents may be crucial in the presence of arterial hypotension. SUMMARY: There is increasing evidence that levosimendan exerts beneficial effects in the treatment of sepsis-induced myocardial and pulmonary dysfunction. Future large-scale multicenter clinical trials are now needed to clarify whether levosimendan improves the overall outcome of patients with sepsis and septic shock.

L4 ANSWER 7 OF 21 MEDLINE on STN  
ACCESSION NUMBER: 2007748459 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 18084975  
TITLE: Inoprotection: the perioperative role of levosimendan.  
AUTHOR: Soeding P E; Royse C F; Wright C E; Royse A G; Angus J A  
CORPORATE SOURCE: Cardiovascular Therapeutics Unit, Department of  
Pharmacology, University of Melbourne, Melbourne, Victoria,  
Australia.  
SOURCE: Anaesthesia and intensive care, (2007 Dec) Vol. 35, No. 6,  
pp. 845-62. Ref: 175  
Journal code: 0342017. ISSN: 0310-057X. L-ISSN: 0310-057X.  
PUB. COUNTRY: Australia  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200802  
ENTRY DATE: Entered STN: 19 Dec 2007  
Last Updated on STN: 6 Feb 2008  
Entered Medline: 5 Feb 2008  
REFERENCE COUNT: 175 There are 175 cited references for this document.

AB Levosimendan is emerging as a novel cardioprotective inotrope.  
Levosimendan augments myocardial contractility by sensitising contractile myofilaments to calcium without increasing myosin adenosine triphosphatase activity or oxygen consumption. Levosimendan activates cellular adenosine triphosphate-dependent potassium channels, a mechanism which is postulated to protect cells from ischaemia in a manner similar to ischaemic preconditioning. Levosimendan may therefore protect the ischaemic myocardium during ischaemia-reperfusion as well as improve the contractile function of the heart. Adenosine triphosphate-dependent potassium channel activation by levosimendan may also be protective in other tissues, such as coronary vascular endothelium, kidney and brain. Clinical trials in patients with decompensated heart failure and myocardial ischaemia show levosimendan to improve haemodynamic performance and potentially improve survival. This paper reviews the known pharmacology of levosimendan, the clinical experience with the drug to date and the potential use of levosimendan as a cardioprotective agent during surgery.

L4 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 3  
ACCESSION NUMBER: 2007:1397127 CAPLUS  
DOCUMENT NUMBER: 148:553251  
TITLE: Levosimendan improves renal  
function in patients with acute decompensated heart

failure: comparison with dobutamine  
AUTHOR(S): Yilmaz, Mehmet Birhan; Yalta, Kenan; Yontar, Can;  
Karadas, Filiz; Erdem, Alim; Turgut, Okan Onur;  
Yilmaz, Ahmet; Tandogan, Izzet  
CORPORATE SOURCE: Department of Cardiology, Cumhuriyet University  
Faculty of Medicine, Sivas, 584140, Turk.  
SOURCE: Cardiovascular Drugs and Therapy (2007), 21(6),  
431-435  
CODEN: CDTHET; ISSN: 0920-3206  
PUBLISHER: Springer  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Levosimendan is a relatively new cardiac inotropic agent with calcium sensitizing activity. This study was conducted to investigate the effects of levosimendan (L) and dobutamine (D) on renal function in patients hospitalized with decompensated heart failure (HF). The present study included 88 consecutive patients hospitalized with acutely decompensated HF (New York Heart Association (NYHA) Class 3-4) requiring inotropic therapy. Patients were randomized 2:1 to either L or D for i.v. inotropic support. Diuretic therapy was kept constant during infusions. Renal function values, including serum creatinine (CR), blood urea nitrogen, 24-h urinary output levels and calculated glomerular filtration rate (GFR) were measured just prior to and 24 h after the infusions in all patients, and 48 and 72 h after the infusions in every second patient in both groups. The pre and post-infusion values of renal function and left ventricular ejection fraction (LVEF) were evaluated. LVEF increased significantly in both groups. Those in L showed a significant improvement in calculated GFR after 24 h, whereas those in D showed no significant change (median in change in L: +15.3%, median change in D: -1.33%). Furthermore, in the L group a significant improvement was observed in calculated GFR after

72

h compared to baseline levels, whereas in D no significant change (median change in L: +45.45%, median change in D: +0.09%) was seen. Both agents improved 24-h urinary output. Levosimendan seems to provide beneficial effects in terms of improvement in renal function compared to dobutamine in patients with heart failure who require inotropic therapy.

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD  
(4 CITINGS)  
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 2007:856932 CAPLUS

DOCUMENT NUMBER: 148:69496

TITLE: Levosimendan Improves Renal  
Function in Patients With Advanced Chronic Heart  
Failure Awaiting Cardiac Transplantation

AUTHOR(S): Zemljic, Gregor; Bunc, Matjaz; Yazdanbakhsh, Aria P.;  
Vrtovec, Bojan

CORPORATE SOURCE: Advanced Heart Failure and Transplantation Center,  
Division of Cardiology, Ljubljana University Medical  
Center, Ljubljana, Slovenia

SOURCE: Journal of Cardiac Failure (2007), 13(6), 417-421  
CODEN: JCFAF9; ISSN: 1071-9164

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Long-term impact of levosimendan on renal function remains undefined. Prospectively, we evaluated effects of levosimendan on renal function in patients with advanced chronic heart failure awaiting cardiac transplantation. Methods and

Results: Of 40 patients, 20 were randomized to receive levosimendan (10-min bolus 12 µg/kg, followed by 0.1 µg/kg/min for 24 h; LS Group), and 20 received no levosimendan (Controls). The groups did not differ in age, heart failure etiol., left ventricular ejection fraction, and plasma brain natriuretic peptide. Patients were followed for 3 mo. At baseline, the groups did not differ in serum creatinine (1.92 ± 0.13 mg/dL in LS Group vs. 1.91 ± 0.12 mg/dL in Controls, P = .81) and creatinine clearance (43.7 ± 2.9 mL/min vs. 43.9 ± 2.8 mL/min, P = .84). At 3 mo, we found a decrease in serum creatinine and an increase in creatinine clearance in LS Group, but not in controls, leading to a significant intergroup difference in serum creatinine (1.60 ± 0.26 mg/dL in LS Group vs. 1.90 ± 0.14 mg/dL in Controls, P = .005) and creatinine clearance (53.6 ± 8.6 mL/min vs. 44.0 ± 3.3 mL/min, P = .005). An improvement in creatinine ≥0.5 mg/dL occurred in 50% patients from LS Group compared with 10% of controls (P = .005).  
 Conclusions: Levosimendan improves long-term renal function in advanced chronic heart failure patients awaiting cardiac transplantation.

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)  
 REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 21 MEDLINE on STN  
 ACCESSION NUMBER: 2007721620 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 18030611  
 TITLE: Levosimendan improves renal function in acute decompensated heart failure: cause and clinical application. Editorial to: "Levosimendan improves renal function in patients with acute decompensated heart failure: comparison with dobutamine by Yilmaz et al."  
 AUTHOR: Damman K; Voors A A  
 SOURCE: Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy, (2007 Dec) Vol. 21, No. 6, pp. 403-4. Journal code: 8712220. ISSN: 0920-3206. L-ISSN: 0920-3206.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Commentary (COMPARATIVE STUDY) Editorial  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200802  
 ENTRY DATE: Entered STN: 11 Dec 2007  
 Last Updated on STN: 16 Feb 2008  
 Entered Medline: 15 Feb 2008

L4 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 5  
 ACCESSION NUMBER: 2007:511631 CAPLUS  
 DOCUMENT NUMBER: 147:157307  
 TITLE: Effect of severe renal failure and haemodialysis on the pharmacokinetics of levosimendan and its metabolites  
 AUTHOR(S): Puttonen, Jaakko; Kantele, Sampo; Kivikko, Matti; Hakkinen, Sari; Harjola, Veli-Pekka; Koskinen, Petri; Pentikainen, Pertti J.  
 CORPORATE SOURCE: Clinical R+D, Orion Pharma, Kuopio, Finland  
 SOURCE: Clinical Pharmacokinetics (2007), 46(3), 235-246 CODEN: CPKNDH; ISSN: 0312-5963  
 PUBLISHER: Wolters Kluwer Health  
 DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background and objectives: Levosimendan is a calcium sensitizer developed for the treatment of congestive heart failure. It increases myocardial contractility, reduces the filling pressure and dilates both the peripheral and coronary vessels. The circulating metabolites of levosimendan, OR-1855 and OR-1896, are formed and eliminated slowly after i.v. administration of levosimendan. The aim of this study was to investigate the effect of impaired renal function and hemodialysis on the pharmacokinetics of levosimendan, OR-1855 and OR-1896. Study design: This study was an open-label, nonrandomized, phase I pharmacokinetic study. Levosimendan was administered as a single-dose infusion of 0.1 µg/kg/min for 24 h. The follow-up period lasted 3 wk. Study setting: Twenty-five patients were included: 12 patients with severe chronic renal failure (CRF) with creatinine clearance of <30 mL/min/1.73m<sup>2</sup> and 13 patients with end-stage renal disease (ESRD) undergoing hemodialysis. A group of 12 healthy subjects served as controls. Results: Levosimendan, the parent drug, was eliminated rapidly from the plasma after discontinuation of its infusion, with an elimination half-life (t<sub>1/2</sub>) [mean ± standard error of mean] of 1.5 ± 0.09 h in ESRD patients undergoing hemodialysis, 1.0 ± 0.2 h in patients with severe CRF and 0.91 ± 0.03 h in healthy subjects. The t<sub>1/2</sub> of levosimendan was significantly longer (p < 0.001) in ESRD patients undergoing hemodialysis than in healthy subjects. The t<sub>1/2</sub> of OR-1855 and OR-1896 were 94.0 ± 20.4 h and 96.5 ± 19.5 h, resp., in ESRD patients undergoing hemodialysis compared with 60.8 ± 5.2 and 61.6 ± 5.2 h, resp., in healthy subjects (p = not significant). The t<sub>1/2</sub> of OR-1855 was significantly longer (85.0 ± 13.6 h) in patients with severe CRF than in healthy subjects (60.8 ± 5.2 h, p < 0.05). The area under the plasma concentration-time curve (AUC) and the peak plasma concentration (C<sub>max</sub>) of the metabolites were approx. 2-fold in patients with ESRD undergoing hemodialysis and patients with severe CRF compared with healthy subjects. The mean unbound fraction (f<sub>u</sub>) of levosimendan in plasma was approx. 2% in each study group, whereas the f<sub>u</sub> of the metabolites was considerably higher (63-70%). In contrast to levosimendan, the metabolites were dialyzable, with dialysis clearance of approx. 100 mL/min. The hemodynamic responses and adverse event profiles were similar in the study groups, with headache, palpitations and dizziness being the most frequently recorded adverse events. Conclusion: The t<sub>1/2</sub> of the levosimendan metabolites was prolonged 1.5-fold and their AUC and C<sub>max</sub> were 2-fold in patients with severe CRF and ESRD patients undergoing hemodialysis as compared with healthy subjects. These results suggest that the dose should be reduced when levosimendan is used for the treatment of congestive heart failure in patients with severe renal insufficiency.

OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)  
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 6  
ACCESSION NUMBER: 2006:583839 CAPLUS  
DOCUMENT NUMBER: 145:117083  
TITLE: Levosimendan protects against experimental endotoxemic acute renal failure  
AUTHOR(S): Zager, Richard A.; Johnson, Ali C.; Lund, Steve; Hanson, Sherry Y.; Abrass, Christine K.  
CORPORATE SOURCE: Department of Medicine, University of Washington, Seattle, WA, USA  
SOURCE: American Journal of Physiology (2006), 290(6, Pt. 2), F1453-F1462  
CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Endotoxemia induces a hemodynamic form of acute renal failure (ARF; renal vasoconstriction ± reduced glomerular ultrafiltration coefficient, K<sub>f</sub>; minimal/no histol. damage). We tested whether levosimendan (LS), an ATP-sensitive K<sup>+</sup> (KATP) channel opener with cardiac inotropic and possible anti-inflammatory properties, might have utility in combating this form of ARF. CD-1 mice were injected with LPS ± LS. LS effects on LPS-induced systemic inflammation (plasma TNF- $\alpha$ /MCP-1; cardiorenal mRNAs), plasma NO levels, and azotemia were assessed. Because KATP channel opening has been reported to mediate hypoxic tubular injury, possible adverse LS effects on ischemic ARF and ATP depletion injury were sought. Effects of diazoxide (another KATP channel agonist) and glibenclamide (a channel antagonist) on hypoxic tubular injury also were assessed. Finally, the ability of LS to alter rat mesangial cell (MC) contraction in response to ANG II (elevated in sepsis) was tested. LS conferred almost complete protection against LPS-induced ARF, without any apparent reduction in the LPS-induced inflammatory response. Neither LS nor diazoxide altered ATP depletion-mediated tubule injury (in vivo or in vitro). Conversely, glibenclamide induced a marked and direct cytotoxic effect. LS completely blocked ANG II-induced MC contraction, an action likely to increase K<sub>f</sub>. We concluded that (1) LS can confer marked protection against LPS-induced ARF; (2) this likely stems from vasoactive properties, rather than redns. in LPS-induced inflammation; and (3) KATP channel agonists (but not antagonists) appear to be devoid of toxic proximal tubular cell effects. This suggests that LS, and other KATP channel agonists, have a margin of safety if employed in situations (sepsis syndrome, heart failure) in which severe renal vasoconstriction might lead to ischemic ARF.

OS.CITING REF COUNT: 19 THERE ARE 19 CAPLUS RECORDS THAT CITE THIS RECORD (19 CITINGS)  
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 21 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:1314266 CAPLUS

DOCUMENT NUMBER: 144:32242

TITLE: Methods, which include the use of a levosimendan compound, for treating a mammal before, during and after cardiac arrest

INVENTOR(S): Weil, Max H.; Sun, Shije; Tang, Wanchun; Delgado-Herrera, Leticia; Padley, Robert J.

PATENT ASSIGNEE(S): Abbott Laboratories, USA

SOURCE: PCT Int. Appl., 75 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
-----	----	-----	-----	-----
WO 2005117884	A1	20051215	WO 2005-US18923	20050527
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,			

AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,  
 EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,  
 RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,  
 MR, NE, SN, TD, TG

AU 2005249498	A1	20051215	AU 2005-249498	20050527
AU 2005249498	B2	20100624		
CA 2568393	A1	20051215	CA 2005-2568393	20050527
US 20060293395	A1	20061228	US 2005-139344	20050527
EP 1758584	A1	20070307	EP 2005-754998	20050527

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,  
 IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR

CN 101031302	A	20070905	CN 2005-80025479	20050527
BR 2005011633	A	20080102	BR 2005-11633	20050527
JP 2008501033	T	20080117	JP 2007-515449	20050527
ZA 2006009895	A	20081029	ZA 2006-9895	20061127
MX 2006013825	A	20070301	MX 2006-13825	20061128
KR 2007035517	A	20070330	KR 2006-7027456	20061227
IN 2006MN01622	A	20080815	IN 2006-MN1622	20061227

PRIORITY APPLN. INFO.:  
 US 2004-575765P P 20040528  
 WO 2005-US18923 W 20050527

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB In one embodiment, the invention provides a method for restoring spontaneous circulation in a mammal in cardiac arrest wherein the method comprises the steps of administering CPR and defibrillation shocks to the mammal as well as a therapeutic amount of a levosimendan compound. Preferably, the levosimendan compound is levosimendan or a metabolite of levosimendan and is administered at the onset of CPR. In another embodiment, the invention provides a method for reducing the frequency and energy of defibrillation shocks applied in cardiac arrest by administering a levosimendan compound prior to applying the defibrillation shocks. The invention also provides a method of treating myocardial dysfunction during or after resuscitation and protecting organ function subsequent to cardiac arrest by using a levosimendan compound. Addnl., the invention provides a method for treating cardiac arrhythmia by applying one or more defibrillation shocks and a therapeutic amount of a levosimendan compound. Pharmaceutical compns. comprising levosimendan useful for such treatment also are disclosed.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:1220694 CAPLUS

DOCUMENT NUMBER: 143:452873

TITLE: A method for the prevention of thromboembolic disorders

INVENTOR(S): Haikala, Heimo; Levijoki, Jouko; Pollesello, Piero; Tilgmann, Carola

PATENT ASSIGNEE(S): Orion Corporation, Finland

SOURCE: PCT Int. Appl., 20 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
-----	----	-----	-----	-----
WO 2005107757	A2	20051117	WO 2005-FI220	20050512
WO 2005107757	A3	20060119		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ,			

LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA,  
 NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK,  
 SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,  
 ZA, ZM, ZW  
 RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,  
 AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,  
 EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,  
 RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,  
 MR, NE, SN, TD, TG

AR 50903	A1	20061206	AR 2005-101922	20050511
AU 2005239847	A1	20051117	AU 2005-239847	20050512
AU 2005239847	B2	20100826		
CA 2564033	A1	20051117	CA 2005-2564033	20050512
EP 1744752	A2	20070124	EP 2005-739367	20050512

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,  
 IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, LV, MK

CN 1980673	A	20070613	CN 2005-80014221	20050512
JP 2007537209	T	20071220	JP 2007-512237	20050512
NZ 550814	A	20091030	NZ 2005-550814	20050512
NZ 579537	A	20100528	NZ 2005-579537	20050512
ZA 2006009304	A	20080130	ZA 2006-9304	20061108
KR 2008020930	A	20080306	KR 2006-7023504	20061109
NO 2006005669	A	20061208	NO 2006-5669	20061208
US 20080039467	A1	20080214	US 2007-596064	20071011

PRIORITY APPLN. INFO.:	FI 2004-674	A	20040512
	WO 2005-FI220	W	20050512

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The invention relates to a method for the prevention of thrombotic,  
 embolic and/or hemorrhagic disorders, such as cerebral infarction (stroke)  
 or myocardial infarction, by administering levosimendan or its metabolite  
 (II) or any of their pharmaceutically acceptable salts to a mammal in need  
 of such prevention.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD  
 (2 CITINGS)  
 REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:237406 CAPLUS

DOCUMENT NUMBER: 143:145342

TITLE: Anti-inflammatory effects of levosimendan in  
 decompensated heart failure: Impact on weight loss and  
 anemia

AUTHOR(S): Parissis, John T.; Farmakis, Dimitrios; Kremastinos,  
 Dimitrios T.

CORPORATE SOURCE: Athens, Greece

SOURCE: American Journal of Cardiology (2005), 95(7), 923-924  
 CODEN: AJCDAG; ISSN: 0002-9149

PUBLISHER: Excerpta Medica, Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Repetitive levosimendan administration in patients with  
 decompensated heart failure resulted in a reduction in serum interleukin-6  
 levels until 10 days after the i.v. infusion of the drug. Within the next  
 14 to 20 days, a novel increase in interleukin-6 is encountered, but this  
 increase never reaches the baseline levels observed before to the initial  
 levosimendan administration. During this time, a significant weight loss is  
 also encountered, apparently due to the reduction of congestion. A trend  
 toward an increase in Hb levels was also observed within 7 to 10 days after  
 levosimendan infusion, while after four repetitive administrations,  
 patients with a satisfactory overall response also show a significant Hb  
 increase. Besides the reduction in circulating blood volume and the  
 improvement

in renal function, anemia reduction may be attributed to the anti-inflammatory effects of levosimendan, through the potential improvement of bone marrow resistance to erythropoietin. These and other similar findings may serve as a starting point for randomized clin. trials that will hopefully provide a solid body of evidence on the exact role of levosimendan in improving collateral, inflammation-induced abnormalities, such as cachexia and anemia, in patients with chronic heart failure.

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)  
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 7

ACCESSION NUMBER: 2005:953092 CAPLUS

DOCUMENT NUMBER: 144:122044

TITLE: Cardiac and Renal Effects of

Levosimendan, Arginine Vasopressin, and  
Norepinephrine in Lipopolysaccharide-treated Rabbits  
AUTHOR(S): Faivre, Valerie; Kaskos, Husam; Callebort, Jacques;  
Lossier, Marie-Reine; Milliez, Paul; Bonnin, Philippe;  
Payen, Didier; Mebazaa, Alexandre

CORPORATE SOURCE: Department of Anesthesiology and Critical Care  
Medicine, Institut Federatif de Recherche 06, Hopital  
Lariboisiere, Paris, 75475, Fr.

SOURCE: Anesthesiology (2005), 103(3), 514-521

CODEN: ANESAV; ISSN: 0003-3022

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Because sepsis-induced myocardial dysfunction related to sepsis is at least partially related to a decrease in cardiac myofilament response to calcium, the use of the new myofilament-calcium sensitizer, levosimendan, has been proposed. In addition, arginine vasopressin is increasingly proposed as a vasopressor in septic patients, although data on its effects on cardiac function are still scarce. The aim of the current study was to assess, invasively and noninvasively, whether levosimendan, arginine vasopressin, and norepinephrine, either alone or combined, may modify sepsis-induced myocardial dysfunction and renal hemodynamics. Methods: Thirty-six hours after lipopolysaccharide or saline administration, rabbits were studied either after slight sedation for echocardiog. or after general anesthesia with sodium pentobarbital for the following measurements: aortic flow velocity and maximum acceleration of blood flow in the ascending aorta and renal macrocirculation and microcirculation. Results: Levosimendan improved, within 30 min of administration, both maximum acceleration of blood flow by  $20 \pm 12\%$  ( $n = 8$ ;  $P < 0.05$ ) and left ventricular shortening fraction by a similar extent. Furthermore, low doses of arginine vasopressin markedly deteriorated cardiac function via an afterload-independent mechanism, even when animals were pretreated with levosimendan, whereas norepinephrine showed no detrimental effects on cardiac function. The study also showed that norepinephrine often improved renal medullary blood flow, whereas arginine vasopressin consistently decreased it. Conclusion: Levosimendan and norepinephrine both exert beneficial effects in endotoxemic animals and should be further explored in human sepsis trials.

OS.CITING REF COUNT: 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 21 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2004:589420 CAPLUS

DOCUMENT NUMBER: 141:82329

TITLE: levosimendan and active metabolite for  
 treatment of renal failure in mammals  
 INVENTOR(S): Kivikko, Matti; Haikala, Heimo  
 PATENT ASSIGNEE(S): Orion Corporation, Finland  
 SOURCE: PCT Int. Appl., 13 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004060375	A1	20040722	WO 2004-FI2	20040102
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ				
CA 2511735	A1	20040722	CA 2004-2511735	20040102
EP 1581227	A1	20051005	EP 2004-700048	20040102
EP 1581227	B1	20070228		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
AT 355063	T	20060315	AT 2004-700048	20040102
JP 2006515348	T	20060525	JP 2006-500147	20040102
PT 1581227	E	20070330	PT 2004-700048	20040102
ES 2281775	T3	20071001	ES 2004-700048	20040102
US 20060166994	A1	20060727	US 2006-541394	20060329
PRIORITY APPLN. INFO.:			FI 2003-15	A 20030103
			WO 2004-FI2	W 20040102

# ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Levosimendan or its active metabolite are useful in reducing  
 mortality in mammals suffering from renal failure.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD  
 (1 CITINGS)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 21 MEDLINE on STN

ACCESSION NUMBER: 2006173222 MEDLINE

DOCUMENT NUMBER: PubMed ID: 16566697

TITLE: Levosimendan following coronary artery bypass  
 grafting in a patient with end-stage renal  
 failure: a case report.

AUTHOR: Raftopoulos S C

CORPORATE SOURCE: Department of Intensive Care Medicine, Sir Charles Gairdner  
 Hospital, Nedlands, Western Australia..  
 spiro@graduate.uwa.edu.au

SOURCE: Critical care and resuscitation : journal of the  
 Australasian Academy of Critical Care Medicine, (2004 Jun)  
 Vol. 6, No. 2, pp. 109-12.  
 Journal code: 100888170. ISSN: 1441-2772. L-ISSN:  
 1441-2772.

PUB. COUNTRY: Australia

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: NONMEDLINE; PUBMED-NOT-MEDLINE

ENTRY MONTH: 200604

ENTRY DATE: Entered STN: 29 Mar 2006

Last Updated on STN: 22 Apr 2006

Entered Medline: 21 Apr 2006

AB Levosimendan is a novel inotropic agent indicated for patients with

decompensated heart failure. It has well recognised mechanisms of action. Its use however, has not been described in patients with end-stage renal failure. This report describes the use of levosimendan in a post-operative coronary artery bypass graft patient with decompensated heart failure and end-stage renal failure previously receiving dialysis six days per week. Levosimendan proved to be a safe and useful agent when used as a continuous intravenous infusion initially at 0.05 microg/kg/min then increasing up to 0.2 microg/kg/min for a total of 42 hours.

L4 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2004:51937 CAPLUS  
DOCUMENT NUMBER: 140:350704  
TITLE: Vasoactive drugs and the kidney  
AUTHOR(S): Lee, Raymond Wai Chuen; Di Giantomasso, David; May, Clive; Bellomo, Rinaldo  
CORPORATE SOURCE: Department of Intensive Care and Department of Medicine, Florey Institute of Physiology, Austin Hospital, Melbourne, Australia  
SOURCE: Best Practice & Research, Clinical Anaesthesiology (2004), 18(1), 53-74  
CODEN: BPRCD8  
PUBLISHER: Elsevier Science B.V.  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English

AB A review. Protection of renal function and prevention of acute renal failure (ARF) are important goals of resuscitation in critically ill patients. Beyond fluid resuscitation and avoidance of nephrotoxins, little is known about how such prevention can be achieved. Vasoactive drugs are often administered to improve either cardiac output or mean arterial pressure in the hope that renal blood flow will also be improved and, thereby, renal protection achieved. Some of these drugs (especially low-dose dopamine) have even been proposed to have a specific beneficial effect on renal blood flow. However, when all studies dealing with vasoactive drugs and their effects on the kidney are reviewed, it is clear that none were demonstrated to achieve clin. important benefits in terms of renal protection. It is also clear that, with the exception of low-dose dopamine, there were no randomized controlled trials of sufficient statistical power to detect differences in clin. meaningful outcomes. In the absence of such data, all that is available is based on limited physiol. gains (changes in renal blood flow or urine output) with one or another drug in one or another subpopulation of patients. Furthermore, given the authors' lack of understanding of the pathogenesis of ARF, it is unclear whether hemodynamic manipulation is an appropriate avenue to achieve renal protection. There is a great need for large randomized controlled trials to test the clin., instead of physiol., effects of vasoactive drugs in critical illness.

OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)  
REFERENCE COUNT: 96 THERE ARE 96 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2003:319257 CAPLUS  
DOCUMENT NUMBER: 138:343856  
TITLE: Buccal sprays or capsules containing cardiovascular or renal drugs  
INVENTOR(S): Dugger, Harry A., III  
PATENT ASSIGNEE(S): USA  
SOURCE: U.S. Pat. Appl. Publ., 15 pp., Cont.-in-part of U.S. Ser. No. 537,118.  
CODEN: USXXCO

DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 19  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20030077229	A1	20030424	US 2002-230075	20020829
WO 9916417	A1	19990408	WO 1997-US17899	19971001
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
EP 1036561	A1	20000920	EP 2000-109357	19971001
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1952802	A2	20080806	EP 2007-23005	19971001
EP 1952802	A3	20090617		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
EP 2042161	A1	20090401	EP 2008-20267	19971001
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CA 2496769	A1	20040311	CA 2003-2496769	20030827
WO 2004019909	A2	20040311	WO 2003-US26853	20030827
WO 2004019909	A3	20040708		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003270014	A1	20040319	AU 2003-270014	20030827
EP 1536769	A2	20050608	EP 2003-751909	20030827
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
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PRIORITY APPLN. INFO.:			WO 1997-US17899	A2 19971001
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			EP 1997-911621	A3 19971001
			JP 2000-513555	A3 19971001
			US 2002-230075	A 20020829
			WO 2003-US26853	W 20030827

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Buccal aerosol sprays or capsules using polar and non-polar solvent have now been developed which provide biol. active compds. for rapid absorption through the oral mucosa, resulting in fast onset of effect. The buccal polar compns. of the invention comprise formulation A: aqueous polar solvent, active compound, and optional flavoring agent; formulation B: aqueous polar

solvent, active compound, optionally flavoring agent, and propellant; formulation C: non-polar solvent, active compound, and optional flavoring agent; and formulation D: non-polar solvent, active compound, optional flavoring agent, and propellant. Thus, a polar lingual spray contained isoproterenol-HCl 0.5-6, water 50-75, EtOH 5-10, PEG 5-15, sorbitol 0.4-1.0, aspartame 0.04-0.1, and flavors 2-3%.

L4 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 8

ACCESSION NUMBER: 1996:619297 CAPLUS

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TITLE: Influence of levosimendan, pimobendan, and milrinone on the regional distribution of cardiac output in anesthetized dogs

AUTHOR(S): Pagel, Paul S.; Hettrick, Douglas A.; Warltier, David C.

CORPORATE SOURCE: Dep. Anesthesiol., Med. Coll. Wisconsin, Milwaukee, WI, 53226, USA

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AB The distribution of cardiac output during administration of levosimendan, a new myofilament calcium sensitizer, is unknown. The authors examined and compared the effects of levosimendan, pimobendan, and milrinone on regional tissue perfusion by use of the radioactive microsphere technique in barbiturate-anesthetized dogs. Hemodynamics and regional blood flow were determined before and during infusions of levosimendan (0.75, 1.5, and 3.0  $\mu\text{g kg}^{-1} \text{ min}^{-1}$ ), pimobendan (10, 20, and 40  $\mu\text{g kg}^{-1} \text{ min}^{-1}$ ), or milrinone (1.0, 2.0, and 4.0  $\mu\text{g kg}^{-1} \text{ min}^{-1}$ ). All three drugs caused similar increases in heart rate, cardiac output, and left ventricular + dP/dt and decreases in end-diastolic pressure and systemic vascular resistance. No changes in subendocardial, midmyocardial, and subepicardial blood flow occurred during administration of levosimendan. However, a redistribution of blood flow from subendocardium to subepicardium was observed. Pimobendan increased midmyocardial and subepicardial blood flow and reduced the endo/epi ratio to a greater degree than levosimendan. Milrinone did not affect myocardial perfusion. Levosimendan increased blood flow to the renal medulla and decreased renal medullary and cortical vascular resistance. Levosimendan increased blood flow to the small intestine and liver and reduced vascular resistance in these organs. Pimobendan increased hepatic blood flow to a greater degree than levosimendan but did not alter small intestinal perfusion. All three drugs decreased splenic blood flow to similar degrees. Levosimendan and pimobendan reduced cerebral vascular resistance. Levosimendan and milrinone reduced skeletal muscle vascular resistance. The results indicate that levosimendan, pimobendan, and milrinone cause subtly different alterations in regional tissue perfusion while producing similar hemodynamics effects.

OS.CITING REF COUNT: 35 THERE ARE 35 CAPLUS RECORDS THAT CITE THIS RECORD (35 CITINGS)

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